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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/677,116	09/30/2003	Sangita	60023 (50152)	4295

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EXAMINER
CHANDRAKUMAR, NIZAL S

ART UNIT	PAPER NUMBER
1625	

MAIL DATE	DELIVERY MODE
09/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	**Application No.** 10/677,116	**Applicant(s)** SANGITA ET AL.	
	Examiner Nizal S. Chandrakumar	**Art Unit** 1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2007*.
2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8 and 13* is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) *8 and 13* is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.
10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a)☐ All b)☐ Some * c)☐ None of:
1.☐ Certified copies of the priority documents have been received.
2.☐ Certified copies of the priority documents have been received in Application No. _____.
3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application filed 09/30/2003.

Applicants' response filed 07/17/2007 is acknowledged

In a telephone (617-517-5564) conversation with applicants' representative Ms. Jun Umemuro, on 08/20/2007, applicants agreed to cancel claims 1-7, 7-12 and 14-32. Further, Ms. Jin Umemuro, on 08/20/2007 sent to the Examiner a fax copy of "Proposed Amendments to the Claims". Amended claims was filed 08/21/2007.

Claims 8 and 13 are pending.

Response to the Applicants Remarks filed 07/17/2007 is presented following the New Rejections.

New Rejections:

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 8 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tripathi et al. (IN 186459, Filing date 09/01/2001).

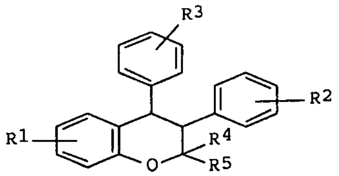
3. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

   1. Determining the scope and contents of the prior art.
   2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

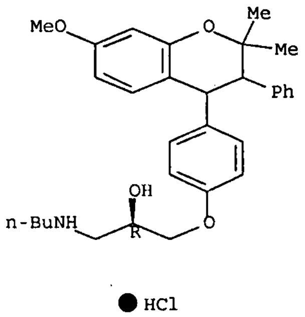
With respect to the compound claim 8,

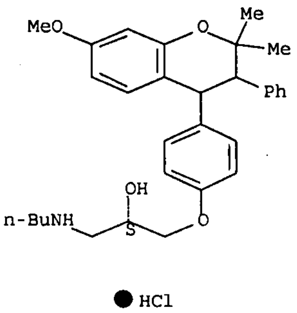
Tripathi et al. teach chroman compounds of the formula I with 'significant activity as antiestrogens and high order of antifertility activity'.

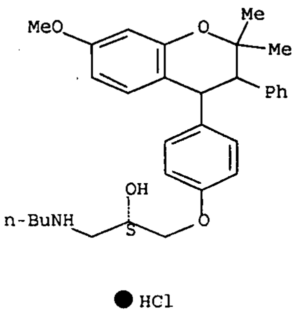


I

with specific examples including the following,







The difference between the prior art compounds and the compounds of the instant claim are that the compounds of the instant claims are stereochemically pure at *all* the stereocenters representing single optical isomers while the compounds of the prior art are mixtures with respect to the stereo centers on the chroman ring system.

It is well known in the art of medicinal chemistry, that single enantiomers of biologically active compounds may provide for more active and/or less toxicity. This is because one isomer of an enantiomeric mixture is likely to have better interaction with biological macromolecules since the later are inherently chiral. For these reasons the experienced Ph.D. medicinal chemist who would make Applicants' compounds, would be motivated to prepare single enantiomers of Tripathi et. al.'s compounds.

One skilled in the art would thus be motivated to prepare products embraced by the prior art to arrive at the instant claimed products with the expectation of obtaining additional beneficial analogs which would have enhanced anti-estrogenic activity with less toxicity. The instant claimed invention would have been suggested and therefore, obvious to one skilled in the art. A strong case of *prima facie* obviousness has been established.

With respect to the method of making claim 13,

Tripathi et al. teach

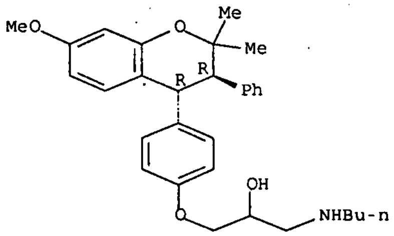
A process for the preparation of the chroman compounds I HX (see above), [R1, R2 = H, alkyl, cycloalkyl, etc.; R3 = 2,3-epoxypropoxy or 3-substituted amino-2-hydroxypropoxy group (OCH2CH(OH)CH2NR6R7; wherein R6, R7 = H, alkyl); R4, R5 = H, alkyl; X = anion such as Cl-] which comprises reacting 2,2-dialkyl-3,4-diarylchromans I [R1, R2, R4, R5 are defined as above; R3 = OH] with chiral epichlorohydrin to give II [R1, R2, R4, R5 are defined as above; R3 = chiral 2,3-epoxypropoxy] followed by treating the latter with alkylamine or cycloalkylamine in a protic solvent such as alkanol and water at a temperature in the range of 30 to 100°C for a period of 15 min to 10 h, to form I [R1, R2, R4, R5 are defined as above; R3 = chiral 3-substituted amino-2-hydroxypropoxy], and recovering and converting the said free base to salt I.HX. Thus, reacting 3,4-trans-2,2-dimethyl-3- phenyl-4-(p-hydroxyphenyl)-7-methoxychroman with (R)-epichlorohydrin (yield 61%) followed by treatment of the resulting intermediate with BuNH2 afforded 60% (R)-3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(3-butylamino-2- hydroxypropoxy)phenyl]-7-methoxychroman hydrochloride.

The difference between the process in the prior art and the process of the instant claim is the phenolic starting material of the prior art is a diastereomeric, racemic mixture while the phenolic starting material of the instant claim is stereochemically pure isomer. Further, the process in the prior art uses protic solvent while the instant case uses aprotic solvent for the reaction.

It is well known in the art, because the chiral centers are located away from the reaction centers, the chirality of the reactants would not have any effect on the kinetics or outcome of the reaction. With respect to the solvent medium, it is well known in the art that because of the high temperature and facile nature of phenolic alkylation reaction, the solvent system would not have major effect on the success of the alkylation with no regards to choice of the solvent. For these reasons the experienced Ph.D. synthetic chemist who would make Applicants' compounds, is likely to use any solvent including the aprotic solvent of the instant case.

4. Claims 8 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Verma et al(Indian Journal of Pharmaceutical Sciences, 1989, 51(2), 48-50).

Verma et al. teach activity of a series of nonsteroidal antiestrogens belonging to the class of 3,4-diaryl chromates and trans-3,4-diaryl chromans with particular reference to



The difference between the prior art compounds and the compounds of the instant claim are that the compounds of the instant claims are stereochemically pure at *all* the stereocenters representing single optical isomers while the compounds of the prior art are mixtures with respect to the stereo center at the carbon containing the hydroxyl group.

It is well known in the art of medicinal chemistry, that single enantiomers of biologically active compounds may provide for more active and/or less toxicity. This is because one isomer of an enantiomeric mixture is likely to have better interaction with biological macromolecules since the later are inherently chiral. For these reasons the experienced Ph.D. medicinal chemist who would make Applicants' compounds, would be motivated to prepare single enantiomers of Verma et. al.'s compounds.

One skilled in the art would thus be motivated to prepare products embraced by the prior art to arrive at the instant claimed products with the expectation of obtaining additional beneficial analogs which would have enhanced anti-estrogenic activity with less toxicity. The instant claimed invention would have been suggested and therefore, obvious to one skilled in the art. A strong case of *prima facie* obviousness has been established.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

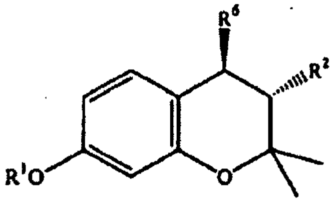
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 13 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a few compounds of the formula V containing limited number of variables, does not reasonably provide enablement for the wide variety of compounds of the formula V. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the process of making the compounds of the claim commensurate in scope with the claim. For instance, the specification while enabling for the process of preparing compounds of Formula V wherein R2 is unsubstituted phenyl , is not enabling for making compounds of the formula V wherein R2 is a substituted phenyl.

The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the relevant factual considerations.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)).

The nature of the invention: The claim is drawn to the process of preparing chroman compounds of formula,



-R^1 is H or C1-C6 alkyl; C3-C7 cycloalkyl; R^2 is phenyl, optionally substituted with 1 to 5 substituents independently selected from the group comprising OH, C1-C6 -alkyl, halogen, nitro, cyano, SH, SR^4, trihalo-Cl-C6–alkyl, Cl-C6 – alkoxy and phenyl, wherein R^4 is Cl-C6 alkyl; and R^6 is phenyl substituted with a hydroxy substituents at C2, C3 or C4,

The breadth of the claims: With the independently varying, three variables layered with substituents on top of substituents, not to mention the stereo chemical possibilities arising because of substitutions on alkyl carbons, the number of theoretically conceivable compounds for the formula is in billions rendering the scope of the claims large.

The level of the skill in the art: The level of skill in the art is high. However, due to the unpredictability in the art of organic synthesis, it is noted that each embodiment of the invention is required to be individually assessed for viability.

The amount of direction or guidance present: The specification contains direction for making compounds of formula V wherein the substituents on the variables and the variables are limited (see below). For instance guidance is present for making *unsubstituted* R2 phenyl group. Guidance in the form of citation for possible sources for the starting materials or literature citation for making the (un)known starting materials necessary is absent in the specification. The guidance present is useful for varying the amine X wherein R7 and R8 are unfunctionalized.

The presence or absence of working examples. The working example present in the specification are limited to compounds of the formula V, wherein R1 is methyl; R2 is unsubstituted phenyl; R6; R7 and R8 are alkyl or cycloalkyl groups that are not substituted with any groups other than alkyl groups; NR7R8 corresponding to morpholine or piperidine.

Thus the specification does not contain working examples wherein, for instance, the R2 and R6 phenyl groups contain hydroxyl groups, thiol groups, alkoxy groups etc.

The state and the predictability of the art: The state of the prior art is unpredictable as to the ability to achieve the synthesis of compounds of formula V with many of the claimed functionalities. In the absence of prior art teaching, absence of citations (commercial or literature) for the procuring needed starting materials for the preparation of substitutions other than the ones mentioned above, one skilled in the art attempting to make compounds of the present inventions would be faced with undue research burden. The synthesis of compounds of the formula V, with independently varying functionalities, for example, defined for the variables R2 and R6 aromatic groups requires unpredictable chemistry sequences. For instance, to make the compound of formula V wherein R2 contains a hydroxyl group, R6 contains a hydroxyl group and R1 is Hydrogen, one skilled in the art would be faced with a multitude of problems including the procurement of starting materials, the protection strategies to differentiate identical functionalities, regio-control with respect similarly reactive groups etc. The art of organic synthesis is unpredictable and target compounds need to be individually assessed for viability. Thus undue experimentation would be needed to make and use the claimed invention of the instant case.

The quantity of experimentation needed: In the instant case, there is a substantial gap between the compounds demonstrated and the breadth of the claims. Given the direction and working Examples provided in the specification, in order to utilize the invention as claimed, the skilled artisan would be presented with an unpredictable amount of experimentation. The guidance provided in the specification limits the number of possible R1, R2 and R6 groups, what and where the substituents are present on these variables. Consequently, a burdensome amount of research would be required by one of ordinary skill in the art to bridge this gap. The instant disclosure is broad and generic.

Taken together the above factors into consideration, enablement for making the compounds provided in the specification is limited to chroman compounds of the formula V with the following variables: R1 = OCH3; R2 = unsubstituted phenyl; R6 = 4-substituted phenyl; R7 and R8 are alkyl or cycloalkyl groups that are not substituted with any groups other than alkyl groups; NR7R8 corresponding to morpholine or piperidine.

Conclusion: Claims 8 and 13 are rejected.

Response to Applicants' Remarks:

Claim Rejections - 35 USC § 103

The previously presented rejections based on Jacobsen Patents are withdrawn.

Claim Rejections - 35 USC § 102

With respect to Verma's prior art (CA 111:224813), Applicants arguments are persuasive as far as the stereochemical structural difference between Verma's compounds and the compounds of instant claim. Further, the Examiner agrees with the Applicants' remarks as to the generic expectation that the pharmacological properties of single enantiomers would be more beneficial compared to the pharmacological properties of mixtures of stereoisomers (see above). However, in practice, the enhanced potency and reduced toxicity of single enantiomers over mixture of stereoisomers is not always observed. Since the specification of the instant applications fails to provide any evidence of enhanced potency or reduced toxicity of the stereochemically pure compounds of the instant claim (showing of unexpected results), in comparison with the potency and toxicity of the corresponding racemic compounds of the prior art, the rejection is maintained.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nizal S. Chandrakumar whose telephone number is 571-272-6202. The examiner can normally be reached on 8.30 am – 5 pm Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached at 571-272-0867 or Primary Examiner D. Margaret Seaman can be reached at 571-272-0694. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nizal S. Chandrakumar

D. MARGARET SEAMAN
PRIMARY EXAMINER